

REMARKS

Claims 53-60 and 81-110 are pending. Claims 1-52 and 61-80 are canceled. No amendments are proposed.

Rejections Under 35 U.S.C. § 112, First Paragraph; Written Description

Claims 54-60, 81-93, 95-106, and 108-110 were rejected as allegedly failing to comply with the written description requirement. The Examiner stated:

Although the claims read on the nucleic acid and protein compositions with no limitation, the specification does not reasonably convey possession of all HIV envelope genes and proteins. In the specification, Applicant has disclosed a few species of envelope genes and proteins of HIV-1 clades A, B, C, D, E, F and G, but has not disclosed sufficient species of vaccines support [sic] the broadly claimed genus of envelope DNA or proteins of all HIV...Consequently, while the skilled artisan would reasonably conclude Applicant was in possession of envelope genes and proteins of a few HIV-1 strains, such as those of one or two strains of each clade A, B, C, D, E, F and G, there is no indication that Applicant was in possession of all envelope genes and proteins of HIV-1 clades A, V, C, D, E, F and G; neither those of clades H, I, J or K, nor those of O and N group of clades, nor those of non-classified and nor those of an entire HIV genus as broadly claimed.

This rejection is respectfully traversed. The claims are drawn to methods of inducing immune responses against human immunodeficiency virus (HIV) or an HIV epitope in a mammal. The methods include administering to a mammal a nucleic acid composition and a protein composition. The nucleic acid composition includes nucleic acid molecules that encode HIV envelope glycoproteins from more than one type or clade of HIV. The Examiner alleged that the written description is not adequate because the specification does not describe examples from clades H, I, J, K, O, or N of HIV. There is nothing particularly different about clades H, I, J, K, O, or N, as a group, compared to clades A to G as a group. Each clade is a different antigen group and applicants merely chose some examples from A to G to show the feasibility of the claimed methods, partly because these represent the majority of the circulating HIV-1 primary viruses in the world, but not as an exclusive group over other antigenic clades. The methods of

claims 54-60, 81-93, 95-106, and 108-110 employ nucleic acids encoding more than one type of HIV envelope protein (i.e., they are polyvalent). The immunogenic characteristics of each of the component antigens are not of import, and certain proteins/genes are merely given as examples.

The Examiner asserted that the claims fail to comply with the written description requirement, because the claims broadly recite HIV envelope genes or proteins. The fact that the specification does not recite each and every known species of envelope gene and protein is irrelevant, because it is not possession of the specific types of HIV envelope genes and proteins, but their use in combinations of different sets, that is important to the claimed invention.

One reason that conventional vaccines have been unsuccessful is that HIV genes and proteins are so diverse that a single antigen may not suffice to generate broadly reactive immune responses that protect an individual against multiple subtypes. The claims properly encompass antigens of multiple HIV types and the specification provides support for these antigens. See the specification, e.g., page 14, lines 16-26, which describes the use of sequences encoding HIV envelope proteins from multiple subtypes. See also the Examples in the specification beginning at page 23, which describe numerous experiments in which compositions encoding multiple types of envelope proteins were made and used in methods for inducing immune responses. One of skill in the art would understand that the claimed methods include uses of nucleic acids encoding envelope proteins of multiple types and that the methods need not be limited to those exemplified. Accordingly, applicants respectfully request that the rejection of claims 54-60, 81-93, 95-106, and 108-110, under 35 U.S.C. § 112, first paragraph, be withdrawn.

Rejections Under 35 U.S.C. § 112, First Paragraph; Enablement

Claim 53 was rejected as allegedly lacking enablement. According to the Examiner, [i]t is well known in the art that development of [a] therapeutic HIV vaccine remains a challenge (Vandepapeliere 2002)...The potential application of HIV envelope protein as a therapeutic vaccine against chronic HIV infection has been studied with "Vaxsyn", a recombinant envelope subunit gp160 vaccine (Pontesilli 1998). Although early phase I studies showed VaxSyn to be immunogenic and safe, Vaxsyn has failed to show any efficacy in HIV-1 infected individuals in [a] Phase II trial.

This rejection is respectfully traversed. Claim 53 is drawn to a method of treating an individual with Acquired Immune Deficiency Syndrome (AIDS) that includes administering to the individual a pharmaceutical composition including a protein composition. The protein composition includes a plurality of sets of HIV envelope glycoprotein molecules, wherein each set includes an envelope glycoprotein which is from a different type or genetic clade of the envelope glycoproteins of another set.

As the Examiner points out, the state of the art is such that promising vaccine candidates may ultimately prove ineffective. This is precisely where the claimed invention provides utility and advantage: the method of claim 53 employs a polyvalent composition, which allows various types of HIV infections to be treated successfully, e.g., because of the broader spectrum response induced by the composition. Throughout the specification, examples demonstrate the ability of polyvalent vaccines to induce neutralizing immune response in animal models, including primate models, that are known and accepted to be predictable models of human immune responses. The examples show that the administration of polyvalent compositions induces antibodies that neutralize and prevent infection. For example, Example 12 describes experiments in which rhesus macaques were administered DNA compositions encoding a Gag protein and encoding four envelope proteins. Animals were boosted with purified gp120 from four HIV isolates from B, Ba-L, Czm, and E type strains. Sera from the animals were analyzed for neutralizing activity. Sera from animals boosted with protein exhibited far greater neutralizing activity than sera from animals administered DNA only. The results of these assays are depicted in Figures 21A-21C; compare Figures 21B and 21C (DNA and protein administration) to Figure 21A (DNA administration). These results show that administration of a polyvalent protein composition can enhance the immune response to HIV antigens.

The Examiner cites the failure of VaxSyn described by Pontesilli et al. (*AIDS*, 12:473-480, 1998; "Pontesilli") as an example of unpredictability of HIV vaccines. VaxSyn is a recombinant gp160. Pontesilli describe experiments in which VaxSyn was administered to patients alone or with an antiretroviral agent, zidovudine (ZDV). Pontesilli did not use a polyvalent protein composition as recited in claim 53. Therefore, Pontesilli's experiments are

not evidence that a polyvalent composition is ineffective. The other article cited by the Examiner, Vandepapeliere (*Lancet*, 2:353-367, 2002) fails to indicate that uses of polyvalent compositions will be unsuccessful. If anything, the reference suggests the promise of using multiple antigens. See, Vandepapeliere, e.g., at page 360, bridging paragraph from left to right columns, which states, “[p]romising results have been obtained in rhesus monkeys immunized with a combination of gp120 and nef/tat regulatory proteins in the AS02 adjuvant and subsequently challenged intravenously with a highly pathogenic, partially heterologous SHIV...this approach is promising.”

Furthermore, the method of claim 53 is not simply a replica of previously reported methods using a different antigen. As demonstrated by the experimental results presented in the specification, the polyvalent approach is much more effective in eliciting useful immune response in monkeys, which are animals as close to humans as one may use in the laboratory.

Regarding the Examiner's comment that “[i]t is not clear what type of immune response is induced to provide a therapeutic benefit by the claimed HIV envelope proteins...resulting in the ‘inhibition of disease progress,’” applicants note that the specification describes different types of immune responses induced by the compositions and methods of measuring them. See, e.g., page 22, line 1, to page 23, line 5, of the specification, which describes methods for measuring cell-mediated responses such as cytokine release and cytotoxicity, and humoral responses such as neutralizing antibody responses. Detection of immune responses is also described in the Examples.

In view of the foregoing, applicants respectfully request that the Examiner withdraw the rejection for alleged lack of enablement.

Rejections Under 35 U.S.C. § 102

Claims 54-60, 81-90, 93, 97, 109, and 110 were rejected as allegedly anticipated by Barnett et al. (*Vaccine*, 8:869-873, 1997; “Barnett”). This rejection is traversed. Applicants respectfully point the Examiner to the fact that the vaccines used by Barnett were monovalent. Thus, Barnett could not have described administering “a plurality of sets of nucleic acid

molecules” and a “set of isolated HIV envelope proteins” as asserted in the Office Action. For example, please see the caption of Figure 1, and also page 870, right bottom, which describes “CM235, US4, and SF2 groups,” indicating each group of animals was administered a different DNA and a corresponding protein antigen, not sets of DNAs or proteins. Tables 1 and 2 are also consistent with this understanding of the experiment. Therefore, applicants respectfully submit that Barnett does not describe the methods of using polyvalent compositions as claimed. Thus, applicants request withdrawal of the rejection.

Rejections Under 35 U.S.C. § 103

Andre et al.

Claims 54 and 96 were rejected as allegedly obvious over Andre et al. (*J. Virol.*, 72(2):1497-1503, 1998; “Andre”) because Andre describes a gp120 DNA sequence with optimized codons. This rejection is respectfully traversed. Andre does not teach or suggest using a plurality of nucleic acid molecules encoding envelope proteins and a set of HIV envelope proteins, and nothing in Andre would motivate one skilled in the art to do so. Thus, applicants request withdrawal of this rejection.

Barnett et al. and Gao et al.

Claim 54, in part, and claims 91, 92, 94, 95, 97, and 98 were rejected as allegedly obvious over Barnett (discussed above) and Gao et al. (*J. Virol.*, 70(3): 1651-1667, 1996; “Gao”). Applicants respectfully traverse.

As discussed above, Barnett fails to disclose or even suggest methods of using compositions encoding multiple types of envelope proteins. According to the Examiner, Gao discloses a panel of envelope genes from HIV-1 clades A-G and suggests that the panel should prove valuable for an AIDS vaccine. However, nothing in Gao would motive one to practice the claimed methods. Gao merely describes the cloning and analysis of envelope genes from various HIV isolates. Gao, very generally, says that the panel of envelope genes described in the reference is valuable for future study and “AIDS vaccine development efforts” (Gao, Abstract,

last sentence). However, Gao does not disclose or suggest any particular methods of using multiple nucleic acids encoding envelope proteins, together in sets as recited in Applicants' claims.

Furthermore, until applicants provided solid evidence that polyvalent vaccines are effective, the prior art provided no indication that polyvalent vaccines would elicit useful immune responses. The work described in the present application clearly demonstrates the technical feasibility and efficacy of the claimed methods, something not at all apparent from the cited prior art.

In view of the foregoing, applicants respectfully request that the Examiner withdraw the rejection of claims 54, 91, 92, 94, 95, 97, and 98, under 35 U.S.C. § 103.

CONCLUSION

Applicants submit that the claims are in condition for allowance and such action is requested. Enclosed is a check for the Petition for Extension of Time fee. Please apply any other charges or credits to deposit account 06-1050, referencing attorney docket no. 17738-003001.

Respectfully submitted,

Date: May 15, 2006

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